Eur J Cancer, Vol. 28, No. 2/3, pp. 626–629, 1992.
Printed in Great Britain

0964–1947/92 $5.00 + 0.00

Ductal Carcinoma *in-situ* of the Breast; Second EORTC Consensus Meeting*

J.A. van Dongen, R. Holland, J.L. Peterse, I.S. Fentiman, M.D. Lagios, R.R. Millis and A. Recht

INTRODUCTION

IN NOVEMBER 1988 experts in the diagnosis and treatment of breast cancer from Europe and North America gathered outside Amsterdam under the auspices of the EORTC Breast Cancer Cooperative Group to discuss what was then known about ductal carcinoma *in situ* (DCIS) [1]. Since that meeting, numerous publications have appeared regarding all aspects of this entity, and national and international cooperative trial organisations have continued to conduct prospective studies of its management. Therefore, it was felt appropriate to hold another meeting preceding the 5th Breast Cancer Working Conference of the EORTC in Leuven, Belgium, in order to summarise what had been learned about DCIS since 1988 and to determine what steps might be taken to obtain the greatest possible information on the remaining questions from the retrospective and prospective studies being conducted in many countries.

The topics discussed during this meeting included: results from screening projects; the pathological and biological features of DCIS and their relationship to clinical management and treatment choice; radiological and histological studies of the distribution and extent of tumour within the breast; assessment of lesion size and margin involvement; criteria of resectability; methodological aspects of ongoing prospective studies; and a review of the results of breast-conserving therapy (BCT) in retrospective series.

During this meeting the participants reached substantial agreement on what is currently known about DCIS with reasonable medical certainty, and what questions remain unanswered. This report summarises their conclusions.

ESTABLISHED FACTS

Some facts concerning DCIS have now been well established (Table 1). DCIS is a proliferation of malignant epithelial cells within ducts and acini, and is distinguished pathologically from infiltrating ductal carcinoma by the absence of light-microscopical evidence of stromal invasion outside the basement membrane.

Table 1. Established facts regarding DCIS

Distinguished from infiltrating ductal carcinoma by the absence of light-microscopical evidence of stromal invasion outside the basement membrane.
Incidence increases when screening mammography is in widespread use.
Not all lesions treated by incomplete biopsy alone will progress to invasive disease.
Lesions are nearly always unicentric, but may still be extensive.
No treatment of regional nodes is warranted.
Heterogeneous
Histologically
Radiologically
Biologically

The prevalence of DCIS increases substantially when mammographical screening becomes widely used in any population. Reviews of the natural history of lesions originally classified as "benign" and treated by biopsy only show that not all these tumours have an equal likelihood of progressing to invasive cancer. Radiological–pathological mapping studies show that DCIS typically does not have a multicentric distribution. The lesion extends within a given region (corresponding with a breast segment), usually without leaving the intervening areas of breast tissue uninvolved. Recurrent lesions are almost invariably at the site of the original DCIS. The incidence of axillary lymph node involvement is negligible (<1%) when adequate specimen evaluation has excluded a significant risk of missing occult micro-invasion; hence, routine nodal treatment is unwarranted and should only be considered for patients with very large DCIS. Finally, DCIS shows remarkable radiological, histological, and biological diversity. Strong correlations between various of these features exist, but so do substantial exceptions to these emerging patterns. Retrospective studies suggest that this diversity may have implications for patient management by BCT, whereas it has little or no relevance when mastectomy is employed.

While these established facts are important, as yet they have only limited impact on the clinical care of patients with DCIS. As discussed below, continued analysis of retrospective studies and, in particular, participation in prospective trials will be necessary before more detailed management schemes can be determined.

EPIDEMIOLOGICAL DATA BASED ON SCREENING PROJECTS

All screening projects with mammography show a substantial increase in the prevalence of DCIS. One subject of particular importance is whether DCIS and infiltrating carcinoma might be related to different epidemiological factors. So far, these

Correspondence to J.A. van Dongen The Netherlands Cancer Institute, Antoni van Leeuwenhoek Huis, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands.
Received 4 Oct. 1991; accepted 24 Oct. 1991.
*This report of the international forum held 2–3 September 1991 by the EORTC was prepared by the writing committee on behalf of the workshop participants: J. Andersen, J.L. Connolly, G. Contesso, I.O. Ellis, V. Eusebi, R. Holland, M.D. Lagios, R.R. Millis, J.L. Peterse, F. Squartini, B. Zafrani (pathologists); L.G. Arnesson, D.M. Barnes, R.W. Blamey, M. Blichert-Toft, J.H. Borger, P. Buytaert, L. Cataliotti, R. Christiaens, M. Coibion, B.F. Cutuli, V. Delledonne, J.A. van Dongen, I.S. Fentiman, A. Fourquet, L. Holmberg, J.P. Julien, R. Kåresen, M. Kaufmann, J.J. Kurtz, J.A. McKinna, H.F. Rauschecker, A. Recht, A. Ringberg, E.J.Th. Rutgers, L.E. Rutqvist, B. Salvadori, E. van der Schueren, M.J. Silverstein, L.J. Solin, H.E. Stegner, A.H. Tulusan (clinicians); J.H.C.L. Hendriks, L. Tabar (radiologists); M. van der Vijver (biologist); B.F. Cohlan, H.J.A. Collette, J. Houghton, I.M. Jackson, F. Mebsout, F. Mignolet, A.B. Miller, B. Sauerbrei, H.J. Stewart, K. van Tongelen (statisticians and epidemiologists).

entities have not been separately analysed. Investigators from both Europe and North America presented intriguing, though preliminary, results regarding the age-specific incidence of DCIS detected at the first and subsequent screening rounds. As is true of invasive cancers, the prevalence of DCIS rises with increasing patient age. However, when the proportion of DCIS among all cancers detected on the first screening is examined, there is disagreement between studies over whether this proportion rises, falls, or is roughly constant with increasing patient age.

PATHOLOGICAL AND BIOLOGICAL STUDIES

The current pathological classification of DCIS into subtypes has been based nearly exclusively on architectural features. This classification was for many reasons considered to be unsatisfactory.

Substantial heterogeneity is commonly encountered within a single case of DCIS. Architectural subtypes may be found either adjacent to or intermingled with one another. The clinical implications of this heterogeneity are not well-known, and can only be assessed from the results of the ongoing BCT studies. It is clear that specimens must be sampled thoroughly so that such heterogeneity can be found and evaluated. However, there is no system currently in use to record this heterogeneity in a simple and reproducible manner. Central pathological review of biopsies of patients initially treated in multiple hospitals have resulted in reclassification rates as high as 30%. Although some disagreements between experts and non-experts are to be expected, nonetheless the ill-defined nature of the current classification system is probably much to blame. This accounts for the varying proportions of DCIS subtypes found in different retrospective studies, which hampers comparison of the results of these studies.

Cytonuclear features, which have been shown to be extremely useful in providing prognostic information for invasive carcinomas, have not been part of the current DCIS classification. Some studies suggest a biological significance for nuclear grade. Therefore, cytonuclear characteristics should be incorporated in the pathological analysis of DCIS, although their significance is not yet fully established.

Promising research is being conducted regarding oncogene activity (of which c-*erb*B-2 has been the most studied) and various techniques of measuring cellular proliferation rates and DNA ploidy.

An increasing body of data suggests a high degree of correlation exists between these pathological, biological and clinical features of DCIS. For example, the comedo subtype is defined on the basis of solid growth pattern and massive necrosis. This architectural finding is usually associated with specific cytonuclear features (large cell, pleomorphic nuclei), specific biological markers (c-*erb*B-2 oncogene amplification), and a particular mammographical presentation (linear and branching calcifications). However, these associations are by no means perfect, and few data are as yet available, to reliably relate any of these features to the results of BCT. Hence, a classification system based on the above mentioned characteristics, dividing DCIS into "comedo" and "non-comedo" subtypes, would be an oversimplification, which might obscure features of possible clinical relevance and should not be used currently as a guide for clinical management.

There was general agreement among pathologists and clinicians that the key to rational patient management with BCT lies in a full understanding of the relationship between features of DCIS and treatment outcome. Hence, a subcommittee of pathologists created a provisional list of features that should be recorded for each case now, in order to aid future retrospective studies (Table 2). Some of these features were believed to be of more immediate clinical use than others (namely, assessments of tumour size and margin involvement, discussed below). Routine investigational use of the new biological markers was strongly endorsed, but practical limitations of availability, cost, and standardisation make it unlikely they can be universally employed for many years to come.

Table 2. Consensus on features to be evaluated in DCIS

Should be described routinely
Tumour size
Margin involvement
Nuclear features
Size
Pleomorphism
Mitoses
Necrosis
Architecture
Description optional
Nuclear features
Chromatin pattern
Nucleoli
Microcalcifications
Host reaction (cellular or stromal)
Additional studies of interest
Oncogenes (especially c-*erb*B-2)
Hormone receptors
Ploidy
Morphometric analysis

ASSESSMENT OF LESION SIZE AND MARGIN INVOLVEMENT

There were substantial differences in the various series in the average lesion size. One reason for this may be the difference in treatment practices between different countries, particularly the indications felt to warrant biopsy of radiological abnormalities. Partly, however, these differences may also arise from the varied definitions and methods used to assess lesion size.

Usually the clinical lesion size is estimated based on the extent of microcalcifications on mammograms or specimen radiographs. Although these measurements are convenient and easily performed, they do not always correspond with the pathological extent of the lesion. In particular, spread of the micropapillary and cribriform architectural subtypes is frequently substantially underestimated. Even with the comedo subtype, more than 15% of tumours may extend further than 2 cm beyond the extent of the microcalcifications seen on specimen radiography.

Pathological assessment of lesion size would, in principle, seem more likely to be clinically relevant than radiological measurements. However, such assessment is neither quick, convenient, nor currently standardised. Uniform spacing between examined sections, maintaining the original orientation of slides with regard to one another, and complete evaluation of all the specimen submitted would be required to determine lesion size accurately.

Even with the problems noted above, assessment of lesion size appears valuable for the current management of patients

with DCIS: a relationship has been demonstrated between lesion size and the likelihood of finding micro-invasive foci. Several investigators have reported that micro-invasion, although not common, occurs with increasing frequency in lesions over 25 mm. Whether lesion size is relevant to the results of BCT is not clear, but it may be a factor of substantial importance. At the least, radiological and pathological descriptions of lesion size are necessary to alert the clinicians to increase their vigilance in any given patient.

It is likely that a critical factor in selecting patients for BCT, either with or without radiotherapy, will be the assessment of the distance and quantity of tumour with respect to the specimen margins. It was felt that the magnitude of the residual tumour burden in the breast depends on the width of the tumour-free margin. However, similar methodological concerns were expressed concerning the assessment and reporting of margin involvement as for lesions size. The definition of what constitute "negative", "close", or "involved" margins has not been established so far. There is insufficient clinical data on BCT to create a conventional definition based on clinical relevance, rather than arbitrary criteria. Hence, there was agreement among both pathologists and clinicians that at present the distance of tumour from inked specimen edges should be quantitatively recorded, rather than employing the subjective terms of "negative" and "close". Also the presence of normal glandular elements between lesion and margin should be recorded.

The importance of margin involvement to the results achieved with BCT when radiotherapy is employed is not clear. Patients in whom tumour cells are found at the edges of resection were universally considered not to be candidates for treatment by surgical excision alone. Hence, assessment of specimen margins is critical in the current management of patients, even if only to exclude certain treatment options.

CRITERIA OF RESECTABILITY

Individual physicians and institutions have formulated criteria of patient evaluation and selection that often differ sharply from one to another. This difference may be seen in the eligibility criteria in the various ongoing national and international prospective BCT studies of DCIS (Table 3). Few data on DCIS supporting the wisdom or relevance of these criteria existed at the time they were formulated.

Most trials require either a microscopically complete excision or excision of all mammographical microcalcifications. These requirements could only be met in 40 to 60% of the patients with DCIS in several series, if BCT with a cosmetically acceptable outcome is the aim. Mastectomy is the therapy of choice for patients with an extensive DCIS, having a cure rate closely approaching 100%.

METHODOLOGICAL ASPECTS OF ONGOING PROSPECTIVE TRIALS

Representatives of all the current European national and international prospective DCIS trials (Table 3) discussed methodological aspects of their studies. Many groups face common problems.

A disturbing trend was noted in many countries relating to patient accrual. Some of these trials have had unusual difficulty recruiting patients with DCIS, even correcting for the slow rate of entry expected in the first year or two of any new study.

Table 3. Summary of ongoing DCIS randomised studies

Group; trial no.	Study coordinator	Eligibility	Treatment; randomisations arms	"Required" No. of patients
1. NSABP B-17 closed	B. Fisher	DCIS with or without LCIS Clear resections margins	Segmental mastectomy with or without RT 50 Gy in 25 fr. whole breast axill. diss. optional	825 (1991—closed for entry)
2. EORTC 10853	I.S. Fentiman	DCIS <5 cm Radical excision	Segmental mastectomy with or without RT 50 Gy in 25 fr. whole breast	188 (1990 decision to enlarge numbers to 1000)
3. U.K. UKCCCR/BCTCS	C.A. Joslin	Screen detected DCIS with or without LCIS Clear resection margins	2 × 2 factorial design Radical excision with or without RT 50 Gy in 25 fr. whole breast with or without TAM	1000
4. Norway	R. Kåresen	DCIS >5 mm <30 mm Radical excision	Radical excision with or without RT 50 Gy in 25 fr. whole breast	?
5. Denmark DBGG 89-IS	M. Blichert-Toft	DCIS with or without LCIS Clear resection margins	Wide segmental resection resp. biopsy for microfocal lesion with or without RT 50 Gy in 25 fr. whole breast	?
6. Sweden	L.E. Rutqvist	DCIS <Quadrant Radicality not necessary	Wide excision (quadrantectomy) with or without RT 50 Gy in 25 fr. whole breast	1000
7. Germany	H. Rauschecker	DCIS <2.5 cm Radical excision	Segmentectomy with or without RT 50 Gy in 25 fr. whole breast	500
8. NSABP-24	B. Fisher	DCIS with or without LCIS Radicality not necessary	Segmental mastectomy with or without RT 50 Gy in 25 fr. with or without TAM axill. diss. optional	1800

Many organisations/centres also include registration studies in the projects: Registration of non-eligible DCIS patients and of patients not willing to participate in the randomised studies. RT, radiotherapy; TAM, tamoxifen.

There appear to be several factors responsible for this. One reason for poor accrual is the various availability of screening mammography within different geographical areas and national health-care systems. Even when mammography is widely used, a fairly large proportion of DCIS cases is considered too large to be treated with BCT. Sometimes lesions originally diagnosed as DCIS are found by central study pathology review to be either benign lesions or invasive carcinomas, but this is accounting for a relatively small proportion of all the ineligible or unentered cases.

A more ominous development seems to be an increasing reluctance by both physicians and patients to accept entry into these trials. The reasons for this appear complex and were much debated. However, all investigators were in agreement that the limited data available on DCIS, particularly with regard to the potential promise (and disadvantage) of BCT, does not warrant dogmatism concerning the merits of the different treatment options, particularly in relation to patient subgroups. Hence, it is important to increase the awareness of both physicians and patients as to the value of the data that will be gathered from these trials and to alert them to how little information there is to support at present any one treatment option as "best".

Much debate has taken place over the years concerning the relative merits of individual national trials versus international trials, both on administrative and scientific grounds. The questions being asked regarding DCIS are increasingly subtle. With so many avenues of investigation ripe for exploration, a large number of cases to analyse is desirable.

The potential benefit of collaboration among the differenc trial groups has been stressed. It is of the utmost importance to establish common terminology and definitions to be able to characterise uniform subgroups from pooled cases from the different trials. Although it will be difficult to establish standardisation in pathological classification and margin assessment (both likely to be critical factors in BCT of DCIS), differences in surgical techniques between the studies may be the hardest factors to evaluate quantitatively or objectively, yet these may be among the most important in explaining differences in outcome between trials. Further study will be needed to determine the best manner of characterising this aspect of BCT. Similar concerns apply to the description of mammographical findings in different trial.

REVIEW OF RETROSPECTIVE STUDIES OF BCT

Several of the participants provided updated information on studies they have published on DCIS since 1988. As noted above, these studies contain important clues regarding possibly important prognostic or selection factors for BCT for DCIS. At present there are too few patients in these series—and too many discrepancies between their results—to justify the formation of detailed guidelines, except for the two (on margins and very extensive tumours) discussed above.

In all series of patients with DCIS treated by BCT, approximately half of the recurrent tumours displayed invasion. Salvage mastectomy in a case of recurrent DCIS might mean only delayed primary treatment if the prognosis of the patient is the same as in the case of immediate mastectomy, resulting in a cure rate of 100%. Salvage surgery for patients with recurrent invasive carcinoma probably will be less effective. The main endpoint of studies of BCT in DCIS should be prevention of deaths from invasive breast cancer, and not just progression to invasion or recurrent DCIS.

The incidence and time-course of local failure are still not well established neither are possible risk factors defined. The preliminary results of the different, usually non-randomised series suggest that the incidence of local recurrence is higher when surgery alone was used, compared with when radiotherapy was added. However, much longer follow-up is needed to substantiate these findings, especially as radiotherapy might be associated with a delay in recurrence, and the median time to recurrence is very long anyway.

Because of the substantial heterogeneity within and between patient populations and treatments in these retrospective studies, these trends could be misleading. In particular, techniques of patient evaluation and selection, surgical technique, and examination of resection margins employed in series with the longest lengths of follow-up were inferior to those used today. This may be particularly critical for those patients treated only with surgery. Nonetheless, even improved techniques might not eliminate these trends; or, quite plausibly, they might have different impacts on different subgroups of patients. Hence, the early results from the current generation of randomised trials will need to be assessed very cautiously because of these findings.

CONCLUSIONS

Much has been learned about DCIS and its management since 1988, but much more work remains to be done. For those attending this meeting, we live at a time in the development of breast cancer therapy which is both exhilarating and frustrating. Exhilarating because of the increasing number of studies being performed and the development of new and promising tools for potential clinical use; frustrating because the increasing number of women brought to our offices as a result of mammography ask many questions we cannot answer. Let us confront this challenge boldly: all efforts should be made to stimulate participation in the prospective trials for all DCIS patients, irrespective of subtypes.

1. Van Dongen JA, Fentiman IS, Harris JR, *et al. Lancet*, 1 July 1989, 25–27.

Acknowledgement—The 2nd EORTC DCIS Consensus Meeting was supported by a grant from the Fourth Medical and Health Research Programme of the Directorate Generale XII of the EC in the frame of "Europe against Cancer".